Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations

Background

Prevalence of Venous Thromboembolism

Pulmonary embolism (PE) resulting from deep vein thrombosis (DVT), collectively known as venous thromboembolism (VTE), affects an estimated 900,000 Americans each year and results in significant morbidity and mortality.[1,2] The average annual incidence of DVT in the United States ranges from 48 to 122 per 100,000.[1,2] With the ageing U.S. population, the number of cases of VTE is likely to rise.

Adverse Consequences of Venous Thromboembolism

There are significant adverse consequences of DVT and PE.[1] Two-thirds of all VTE cases are nonfatal and result in hundreds of thousands of hospitalizations, whereas approximately one-third of these cases are fatal and result in an estimated 300,000 deaths each year.[1,2] The cost of hospitalization for another medical condition has been shown to increase with the diagnosis of DVT (approximately $10,000) or PE ($20,000).[3] Thus VTE is an important patient safety issue that results in significant morbidity, mortality, and health care cost.[4] Accordingly, the comparative effectiveness and safety of interventions for the prevention and treatment of VTE are among the national priorities for comparative effectiveness research.[5]

Pharmacologic Agents and Medical Devices Used for Thromboprophylaxis

There are a number of antithrombotic drugs and antithrombotic mechanical devices that are approved by the U.S. Food and Drug Administration (FDA) for various indications. A small proportion of these are approved for primary prophylaxis of VTE, but others may be considered or used off label for this purpose (Table 1). The pharmacologic agents include unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH; e.g., enoxaparin, dalteparin, and tinzaparin) that are delivered subcutaneously.[6-9] Fondaparinux, a synthetic pentasaccharide, is also available as an option for thromboprophylaxis. We will evaluate drugs and devices that currently are available in the United States and either are FDA approved for VTE prophylaxis or are being used off label for this indication. We will also evaluate the use of antiplatelet agents, such as aspirin and clopidogrel, as well as the anticoagulant warfarin, which may be used off label for this indication. Drugs and devices that do not have FDA approval at present but are likely to gain approval will be systematically identified and evaluated only if they gain regulatory approval in the United States.

LMWHs are known to have better bioavailability after subcutaneous administration, a longer half-life, and a more predictable response and provide flexible outpatient dosing. Because of their decreased binding to platelet factor 4, LMWHs have a lower incidence of thrombocytopenia and heparin-induced thrombocytopenia when compared to UFH. However, UFH and LMWHs differ in their half-life and acquisition cost. Dabigatran is a newly developed oral anticoagulant that directly inhibits thrombin; it has been approved by the FDA for the prevention of stroke in patients with atrial fibrillation. Dabigatran has the potential for off-label use for prophylaxis of VTE. Rivaroxaban is an oral factor Xa inhibitor that was approved by the FDA in July 2011 for VTE prophylaxis among patients undergoing elective hip and knee arthroplasty; this drug also has the potential for off-label use in other patient populations.

Sequential compression devices, venous foot pumps, and various types of inferior vena cava (IVC) filters are also available for use in eligible patients deemed to be at high risk of bleeding when taking anticoagulants or as VTE prophylaxis in patients without an increased bleeding risk.[4]

Definition of Special Populations

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We define special populations as either patients in whom the benefit or risk of VTE prophylaxis is uncertain or patients in whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis and/or significant practice variation due to this uncertainty for this comparative effectiveness review (CER).

Special Populations at Risk for Venous Thromboembolism

The burden of VTE is higher among special populations including patients who have experienced recent trauma[10-15] or burns,[16-18] patients undergoing bariatric surgery,[19-25] and patients with acute renal failure, chronic renal failure, or end-stage renal disease.[26-29] Not only are these special populations at increased risk of DVT and PE, some (i.e., those with trauma, burns, and renal failure) are also at high risk of bleeding, the most important complication of VTE prophylaxis. Furthermore, the risk-benefit ratios of prophylactic medications in certain special populations (i.e., those with renal failure) may be uncertain because of altered clearance of medications.[6-9,30]

General traumatic injuries. Trauma is known to be a major risk factor for VTE. A prospective study reported rates of DVT as high as 58 percent among those who experience severe trauma (injury severity score >9) without thromboprophylaxis.[10] Among hospitalized trauma patients, PE occurs in 1 of every 25 patients and is associated with considerable mortality.[10] Some patients with special types of trauma, such as those with spinal trauma, are at the highest risk of DVT with rates approximating 80 percent.[4]. There appears to be significant practice variation and clinical uncertainty around the role of pharmacologic versus mechanical prophylaxis among patients with trauma. Although pharmacologic prophylaxis is commonly recommended, it may be considered by some physicians to be relatively contraindicated in certain trauma patients such as those with: solid organ injury (i.e., liver, spleen, or kidney); pelvic or retroperitoneal hematoma; ocular injury with hemorrhage; or thrombocytopenia (platelet count <50,000). In these cases, there is debate about the placement of prophylactic IVC filters to prevent PE. Some authors suggest that using this intervention among patients at very high risk may prevent the most dramatic and life-threatening cases of PE, although evidence for this is uncertain. Other studies demonstrate that IVC filters are associated with significant complications,[31,32] such as the occurrence of DVT,[33] and should not be used for this reason. Other studies show that placement of IVC filters does not lower the rate of PE and may not be of benefit in the trauma setting[34] or among other patient populations.[35] Ongoing clinical uncertainty exists about whether prophylactic IVC filters should be used in trauma patients for whom anticoagulation is relatively contraindicatedThe concept of temporary (also known as “retrievable” or “optional”) IVC filters is appealing, yet further complicates the picture. Current guidelines from the American College of Chest Physicians (ACCP) recommend against the use of IVC filters for primary prevention in patients without proven VTE.[4] The Eastern Association for the Surgery of Trauma (EAST) guidelines suggest that prophylactic IVC filters can be considered for use in patients who have certain significant injury patterns, are at very high risk for VTE, and cannot receive pharmacologic prophylaxis.[36]

Traumatic brain injury. There is also considerable practice variation and clinical uncertainty about the choice of a prophylaxis modality (pharmacologic or mechanical) and about the optimal pharmacologic agent, dose, timing of initiation, and duration among patients with traumatic brain injury.[37] This population is at increased risk for or VTE due to a combination of factors (i.e., the brain injury itself, other injuries, intensive care unit admission, immobilization, major surgery, etc.). This risk should prompt routine thromboprophylaxis; however, the associated elevated risk of bleeding in patients with traumatic brain injury often leads physicians to withhold anticoagulant thromboprophylaxis. The concern about anticoagulant thromboprophylaxis in this population is progression of intracranial bleeding that may result in clinical deterioration and possibly worse long-term outcomes. There is ongoing clinical uncertainty and wide variations in practice regarding the appropriate time to initiate pharmacologic prophylaxis. In this CER we will assess the role of pharmacologic versus mechanical prophylaxis, and the optimal time to initiate pharmacologic prophylaxis in hospitalized patients with traumatic brain injury.

Burns. Patients hospitalized with burns are at an increased risk for VTE, but there is no consensus about the most appropriate prophylactic strategy for treating bleeding in these patients.[38] DVT has a

reported incidence of 1 to 23 percent in a series of burn patients.[18] The ACCP guidelines recommend thromboprophylaxis if possible for burn patients who have additional risk factors for VTE such as advanced age, morbid obesity, extensive burns or burns to the lower extremities, concomitant trauma to the lower extremities, use of a femoral venous catheter, and/or prolonged immobility (Grade 1C).[4] However, concerns about the potential risk of heparin-associated bleeding may have resulted in very low rates of heparin use and considerable uncertainty about the optimal choice of therapy among burn centers.[17] There is considerable uncertainty around specific drugs, dosing regimens, and the risk-benefit trade-off for these particular subpopulations of patients.

Liver disease. Patients with liver diseases such as cirrhosis may be simultaneously at increased risk for both bleeding and thrombosis, thus complicating the decisions related to VTE prevention.[39] Patients with thrombocytopenia, platelet dysfunction, and a prolonged international normalized ratio (INR) secondary to liver disease are at increased risk for both minor and major bleeding secondary to altered hemostasis.[40] However, patients with these specific conditions often remain at risk for venous thromboembolism, particularly since many of the illnesses that lead to defects in hemostasis—such as cirrhosis—can directly precipitate thrombosis as a result of activated hemostasis and may also precipitate thrombosis indirectly through complications such as infection. There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population and about the optimal threshold of thrombocytopenia and the prolonged INR value at which bleeding increases with anticoagulant thromboprophylaxis. There are no specific reviews or guidance documents that clarify the role of thromboprophylaxis in these patients.

Antiplatelet therapy. Patients receiving antiplatelet therapy with acetylsalicylic acid or thienopyridines such as clopidogrel, ticlopidine, and prasugrel are at increased risk for bleeding. These patients constitute a large proportion of patients hospitalized for various medical conditions.[39]There is clinical uncertainty about the optimal choice of VTE prophylaxis in this patient population, as some physicians may consider antiplatelets to be sufficient for VTE prophylaxis. There are no specific guidance documents that clarify the role of thromboprophylaxis in this subgroup of patients.

Bariatric surgery. Another population in which there is uncertainty about venous thromboprophylaxis is patients who undergo bariatric surgery. In an analysis of a large cohort in the Bariatric Outcomes Longitudinal Database,[24] the incidence of VTE after bariatric surgery was 0.42 percent within 90 days after surgery. Although these obese patients were at risk of VTE, their hospitalizations were short, and they were able to ambulate early. The risk of VTE was greater in the patients who underwent gastric bypass than in those who underwent adjustable gastric banding (0.55% vs. 0.16%). The risk of VTE was also greater in patients who underwent placement of an IVC filter (hazard ratio 7.66; 95% confidence interval 4.55–12.91). The ACCP guidelines recommend LMWH, low-dose UFH, or fondaparinux at higher than usual doses for patients undergoing bariatric surgery.[4] A recent survey of bariatric surgeons noted their overall preference for using prophylactic medications. Nearly 60 percent of bariatric surgeons preferred LMWH for prophylaxis, but many were uncertain about the best choice of therapy and about the timing and duration of VTE prophylaxis.[19] Therefore, there is much practice variation, ranging from no prophylaxis to multimodality thromboprophylaxis that might also include preoperative placement of an IVC filter.

Obesity and underweight. Obesity, including severe obesity, is associated with an increased risk of VTE.[41] It is uncertain if fixed doses of pharmacologic agents such as UFH, LMWHs, and factor Xa inhibitors provide optimal prophylaxis in this special population. The pharmacokinetics of several agents may be different among obese patients requiring dose adjustments.[42] Although dosage adjustments may be needed for LMWHs and other pharmacologic agents used to treat patients at the extremes of weight, the optimal dosing strategy (including duration of therapy) for these patients is unknown. Similarly, the optimal choice and dosing regimens for patients who are underweight (body mass index <18.5 kg/m^2) is unclear. This lack of clarity has resulted in significant decisional uncertainty about prophylaxis for patients at both extremes of weight. This CER will evaluate the comparative effectiveness and safety of pharmacologic prophylaxis among patients at the extremes of weight and will assess the optimal drugs,

dosages, dose frequency, and duration of pharmacologic prophylaxis during hospitalization of obese and underweight patients.

Acute kidney injury and chronic kidney disease. In a prospective community-based cohort, patients with stage 3 or 4 chronic kidney disease (CKD) had a higher risk of VTE than those with normal kidney function.[26] The rates of VTE among patients with end-stage renal disease were also high. Generally, the burden of VTE among patients with CKD also falls disproportionately on Hispanics and African Americans.[43] Patients with advanced CKD also have a tendency to bleed because of platelet dysfunction.[44] Fondaparinux and LMWHs are primarily eliminated via the renal pathway and may accumulate in patients with renal failure. This accumulation is dependent in part on the chain lengths of the LMWHs and their subsequent renal clearance, thereby resulting in different pharmacokinetic and pharmacodynamic effects.[30] Consequently, patients with diminished renal function may be at an increased risk for adverse events, particularly bleeding. Although there appear to be differences between the LMWHs with regard to accumulation risk, the relationship between their use and the incidence of bleeding is not well established. Current ACCP guidelines recommend that anticoagulant medications that bioaccumulate should be avoided, dose adjusted, or monitored (Grade 1C). Cook et al.[29] argued that LMWHs may be the optimal choice, given the lower incidence of thrombocytopenia in patients with CKD. The optimal treatment choice and dosing strategy for thromboprophylaxis for patients with CKD remains uncertain. There are similar concerns about the optimal strategies for VTE prophylaxis among patients with acute kidney injury. Apart from evaluating the comparative effectiveness and safety of pharmacologic prophylaxis, in our CER we will assess the optimal drugs, dosages, dose frequency, and duration of pharmacologic prophylaxis during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment without dialysis, and patients receiving dialysis.

Systematic Reviews on This Topic

There are no recent relevant CERs that directly address the comparative effectiveness of low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, mechanical devices, and IVC filters or that assesses the dosing strategies for various agents for the populations described above.

Current Practices and Decisional Uncertainty

Some of the special populations we have discussed, such as patients with thrombocytopenia and a prolonged INR secondary to liver disease or those receiving antiplatelet therapy, have not been evaluated in previous guidelines. Additionally, there is considerable decisional uncertainty about the optimal choice of thromboprophylaxis for hospitalized patients with burns, trauma, or traumatic brain injury, patients undergoing bariatric surgery, patients who are obese or underweight, and patients with acute kidney injury and chronic kidney disease.

Expected Use of the Report

The results of the proposed CER will inform developers of professional guidelines for these special populations as the developers make recommendations. The results of the proposed CER are likely to be useful to clinicians and patients in making decisions about the best available options for VTE prophylaxis among these special populations. This CER will also identify those areas in which there is inadequate evidence.

II. The Key Questions

Question 1

a. What is the comparative effectiveness and safety of IVC filters to prevent PE in hospitalized patients with trauma?

Question 2

a. What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with traumatic brain injury?

b. What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent VTE in hospitalized patients with traumatic brain injury?

Question 3

What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with burns?

Question 4

What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients with liver disease?

Question 5

What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in hospitalized patients receiving antiplatelet therapy?

Question 6

What is the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent VTE in patients having bariatric surgery?

Question 7

What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of obese and underweight patients?

Question 8

What is the comparative effectiveness and safety of pharmacologic prophylaxis for prevention of VTE during hospitalization of patients with acute kidney injury, moderate renal impairment, or severe renal impairment not undergoing dialysis and patients receiving dialysis?

Summary of Revisions to Key Questions

The Key Questions were posted on the Effective Health Care Program Web site for public comment and were discussed with the Technical Expert Panel (TEP). The public comments and TEP suggested that mechanical strategies other than prophylactic filters, such as compression stockings and pharmacologic strategies, also be reviewed among hospitalized patients with trauma in addition to our initial question to evaluate the role of inferior vena caval filters in preventing PE. There was uncertainty around the optimal choice of agent for pharmacologic therapy, the timing of its initiation and its relative effectiveness when compared to other mechanical strategies in patients with trauma. Accordingly, we have modified KQ 1 and removed the term “relative contraindication” because it was considered to be too restrictive and heterogeneous. We have included an additional subquestion about the comparison of mechanical versus pharmacologic strategies among hospitalized patients with trauma.

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The public comments and the TEP suggested advised that there were uncertainties about the choice of mechanical versus pharmacologic strategies among patients with traumatic brain injury in addition to issues about timing and duration of pharmacologic prophylaxis. Accordingly, we have modified KQ 2 to include an additional subquestion about the comparison of mechanical versus pharmacologic strategies among patients with traumatic brain injury.

The TEP suggested further clarification of the term “bleeding diathesis.” Since thrombocytopenia has multiple etiologies that made the underlying populations very different with potentially different risk-benefit considerations, we have modified the previous question on patients with bleeding diathesis (originally KQ 4) into two separate questions (now KQ 4 and KQ 5). **]**. KQ 4 considers the role of mechanical versus pharmacologic strategies among hospitalized patients with liver disease. KQ 5 considers the role of mechanical versus pharmacologic strategies among hospitalized patients receiving antiplatelet therapy.

Although there was a suggestion that we also consider the comparative effectiveness and safety of pharmacologic and mechanical strategies to prevent venous thromboembolism in hospitalized patients with trauma , this topic had been adequately covered in previous iterations of the ACCP review and guidelines. [4]The EPC team was also of the view that there was little decisional uncertainity around this particular key question and the team did not feel the need to duplicate the findings of the previous ACCP review, or the update of that review scheduled for release in early 2012.

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Table 2. PICOTS for each Key Question

	KQ 1	KQ 2	KQ 3–KQ 5	KQ 6	KQ 7–KQ 8
Population(s)	• Trauma	• Traumatic brain injury	• Burns (KQ 3) • Liver disease (KQ 4) • Antiplatelet therapy (KQ 5)	• Bariatric surgery	• Obese and underweight patients (KQ 7) • Patients with acute kidney injury or moderate or severe renal impairment (KQ 8) • Patients receiving dialysis (KQ 8)
Interventions (Table 1)	• IVC filters • Mechanical devices • Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors)	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • IVC filters	• Mechanical devices • Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors)	• Pharmacologic (UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices • IVC filters	• Pharmacologic (UFH LMWHs, factor Xa inhibitors, direct thrombin inhibitors) • Mechanical devices
Comparators	• We will evaluate studies that included usual care or those that did not use IVC filters as active controls including mechanical prophylaxis (e.g., SCDs, compression stockings) • We will evaluate placebo-controlled studies, studies that used active controls, and uncontrolled studies.	• We will consider low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • We will evaluate placebo-controlled studies, studies that used active controls, and uncontrolled studies.	• We will consider low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • We will evaluate placebo-controlled studies, studies that used active controls, and uncontrolled studies.	• We will consider low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • We will evaluate placebo-controlled studies, or studies that used active controls, and uncontrolled studies.	• We will consider low-dose UFH, LMWHs, factor Xa inhibitors, direct thrombin inhibitors, and mechanical prophylaxis. • We will evaluate placebo-controlled studies, studies that used active controls, and uncontrolled studies.
Outcomes measures	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality	• Symptomatic DVT • Symptomatic PE • Asymptomatic DVT • Bleeding • Mortality
Adverse effects of intervention(s) and treatment burden	• Major bleeding defined as including: fatal bleeding; clinically overt bleeding causing a fall in hemoglobin of ≥2 g/dL or leading to transfusion of two or more units of packed cells or whole blood; or bleeding into critical organs (retroperitoneal or intracranial)[45] • In surgical patients: an assessment of the amount of blood loss,[46] minor bleeding, surgical site bleeding, and complications from mechanical IVC filters (e.g., device migration, perforation, fractures, filter thrombosis, infections, prolonged hospitalization, mortality)				

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Timings	• Studies with all durations of followup will be included in the analysis. • The length of the evaluation period will be considered when evaluating the benefits and risks (short-term and long-term) for these agents, including the commencement of thromboprophylaxis (preoperatively vs. postoperatively) and the duration of treatment (including that after discharge).				
Settings	• Hospital setting	• Hospital Setting	• Hospital setting	• Hospital setting	• Hospital setting

Abbreviations: DVT = deep vein thrombosis; IVC = inferior vena cava; KQ = key question; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SCD = sequential circumferential compression device; UFH = unfractionated heparin

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Table 1: Pharmacologic agents and medical devices approved in the United States for some indication and that may be considered for VTE prophylaxis

Pharmacologic Agents					
Intervention	Route	Dose	Manufacturer	U.S. Availability	Comments
Antiplatelets					
Aspirin	Oral	Various	Various	Yes	
Clopidogrel (Plavix®)	Oral	75 or 300 mg base	Sanofi Aventis/ Bristol-Myers Squibb	Yes	
Ticlopidine (Ticlid®)	Oral	125 or 250 mg	Hoffman-La Roche Inc.		
Prasugrel (Effient®)	Oral	EQ 5 or 10 mg base	Roche Palo	Yes	
Ticagrelor (Brilinta®)	Oral	90 mg	AstraZeneca LP	Yes	
Dipyridamole (Persantine®)	Oral	25, 50, or 75 mg	Boehringer Ingelheim	Yes	
Cilostazol (Pletal®)	Oral	50 or 100 mg	Otsuka	Yes	
Dextran sulphate				Yes	
Vitamin K Antagonists					
Warfarin (Coumadin®)	Oral	1–10 mg	Various generics; Bristol-Myers Squibb	Yes	
Dicumarol	Oral	Various			
Low-Dose Unfractionated Heparins					
Heparin	Subcutaneous	5,000 Units BID or TID		Yes	
Low-Molecular-Weight Heparins					
Enoxaparin sodium (Lovenox®)	Subcutaneous	40 mg QD or 30 mg BID (30 mg for renal impairment)	Sanofi-Aventis; generic from Sandoz (2010)	1993	Dosing indication for abdominal surgery and acutely ill medical patients
Dalteparin sodium (Fragmin®)	Subcutaneous	5,000 IU QD	Eisai/Pfizer	1994	Indicated for surgery prophylaxis
Tinzaparin sodium (Innohep®)	Subcutaneous	3,500 IU QD to 4500 IU SC daily	LEO Pharma/Celgene	2000	Indicated for surgery prophylaxis
Factor Xa Inhibitors					
Fondaparinux (Arixtra®)	Subcutaneous	2.5 mg QD	GSK	2001	Indicated for abdominal surgery

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					prophylaxis
Rivaroxaban (Xarelto®)	Oral	10 mg QD	Johnson and Johnson	2011	Indicated for elective hip/knee arthroplasty
Direct Thrombin Inhibitors					
Argatroban (Argatroban®)	Intravenous Infusion	100mg/mL	Pfizer	2000	Prophylaxis with active HIT
Dabigatran (Pradaxa®)	Oral	75 and 150 mg	Boehringer Ingelheim	2010	Prevent stroke and systemic embolism in AF
Bivalirudin (Angiomax®)	Intravenous	250 mg/Vial	The Medicines Company	2000	
Lepirudin (Refludin®)	Intravenous Infusion	50 mg/Vial	Bayer	1998	Anticoagulation with HIT to prevent further thromboembolic complications

Mechanical Devices			
Intervention	**Name**	**Manufacturer**	**Comments**
Intermittent Pneumatic compression	Aircast VenaFlow	DJO	Apply intermittent application of pressure to a patient's calf, thigh or foot for the purpose of assisting blood flow in the veins.
	SCD Express	Tyco/Kendall	DVT prophylaxis
Graduated compression stockings	Jobst T.E.D.® Others	Jobst	To prevent pooling of blood in legs
Venous Foot Pumps	A-V Impulse System Venodyne	Novamedix	DVT prophylaxis
Inferior Vena Caval Filters			
Name	**Type**	**Manufacturer**	**Comments**
Greenfield Stainless Steel®	Permanent	Boston Scientific	Prevention of PE with venous thrombosis or pulmonary thromboembolism when anticoagulants are contraindicated
Simon Nitinol®	Permanent	Bard Peripheral Vascular	Preventing PE from migrating to the pulmonary arteries
TRAPEASE®	Permanent	Cordis	Prevention of recurrent PE when anticoagulants are contraindicated
Greenfield Titanium®	Permanent	Boston Scientific	No information available
Vena Tech LP®	Permanent	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
Gianturco-Roehm Bird's Nest®	Permanent	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
Celect®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
Gunther Tulip®	Retrievable	Cook	Prevention of recurrent PE when anticoagulants are contraindicated
G2®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE
G2x®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
Eclipse®	Retrievable	Bard Peripheral Vascular	Prevention of recurrent PE when anticoagulants are contraindicated
VenaTech LGM®	No longer sold	B. Braun	Partial interruption of IVC to prevent PE when anticoagulants are contraindicated
Tempofilter®	Retrievable	B. Braun	
ALN IVC®	Retrievable	ALN Implants	Prevention of recurrent PE when anticoagulants are contraindicated
Option IVC®	Retrievable	Rex/Angio Tech	Prevention of recurrent PE when anticoagulants are contraindicated
Safeflo®	Permanent	Rafael Medical	Prevention of recurrent PE when anticoagulants are contraindicated

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OPTEASE®	Retrievable	Cordis Corp	Prevention of recurrent PE when anticoagulants are contraindicated

Abbreviations: AF = atrial fibrillation; BID = twice a day; DVT = deep vein thrombosis; EQ = equivalent; HIT = heparin-induced thrombocytopenia; IU = international unit; IVC = inferior vena cava; PE = pulmonary embolism; QD = once a day; SC = subcutaneous; TID = three times a day

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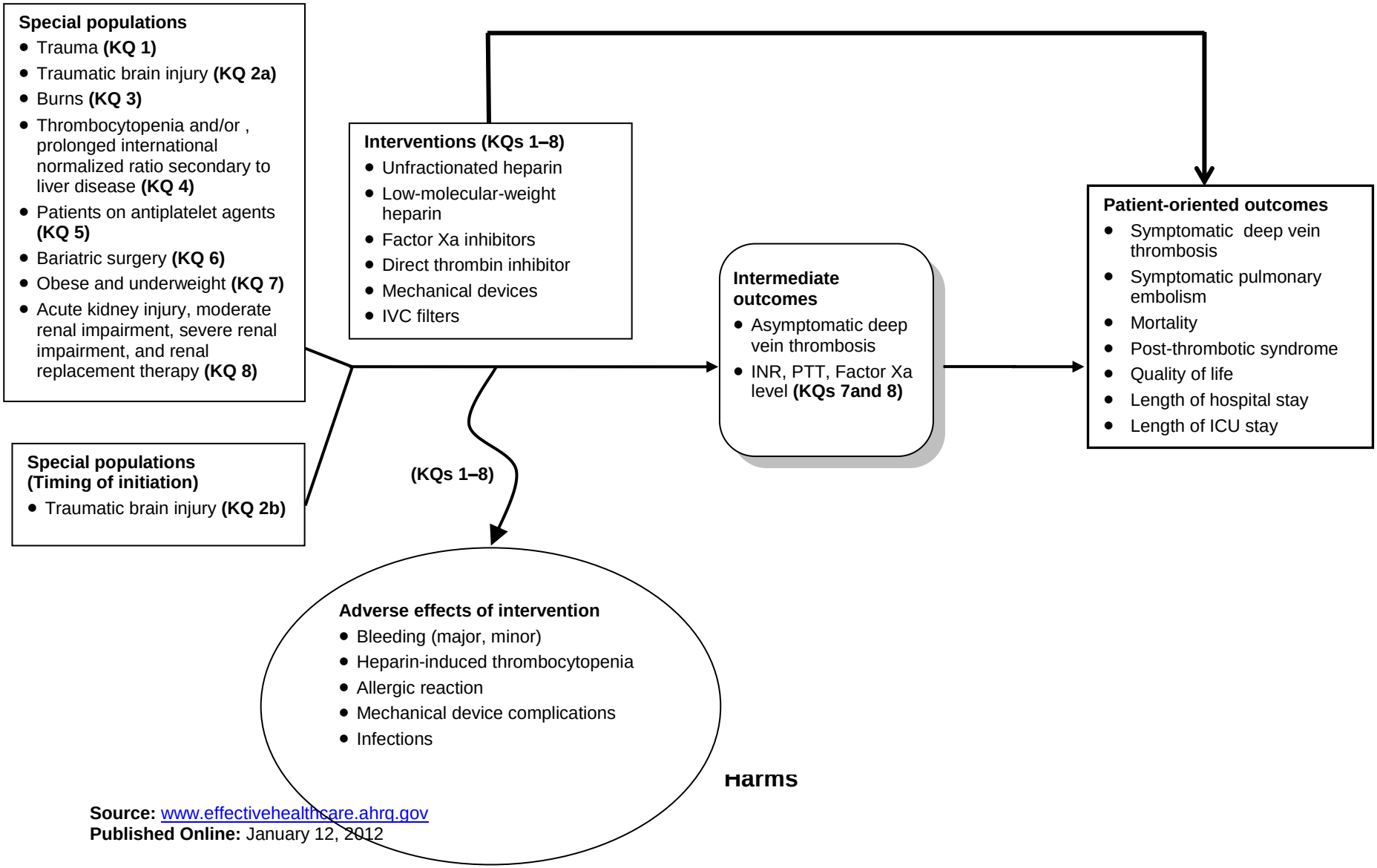
Figure 1. Analytic Framework: Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations



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Abbreviations: IVC = inferior vena cava; KQ = key question

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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Table 3: List of Inclusion/Exclusion Criteria

Inclusion	Exclusion
• Human subjects (only)	• Animal studies/models
• Adults in special patient populations, including: ○ Trauma ○ Traumatic brain injury ○ Burns ○ Liver disease ○ Antiplatelet therapy ○ Bariatric surgery ○ Obese and underweight ○ Acute kidney injury, moderate renal impairment, severe renal impairment, renal replacement therapy	• Children • Pediatric • Adolescent • Adults in the following patient populations: ○ Treatment of VTE ○ Secondary prophylaxis ○ Catheter thrombosis ○ Antiphospholipid antibodies/other autoimmune diseases ○ Cancer (malignancy, chemotherapy, radiotherapy) ○ Cardiovascular (coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty) patients on full-dose anticoagulation ○ Pregnancy ○ Disseminated intravascular coagulation ○ Heparin-induced thrombocytopenia ○ Congenital platelet disorders ○ VTE prophylaxis for long distance travel ○ Abdominal surgery ○ Vascular surgery ○ Urological surgery ○ Gynecological surgery
We will include the following study designs* ○ Randomized controlled trials ○ Prospective cohort studies ○ Retrospective cohort studies ○ Case-control studies ○ Uncontrolled case-series for devices ○ Case reports of device complications in the relevant special populations ○ Case reports of pharmacologic therapies other than the known complications of bleeding and heparin-induced thrombocytopenia	• Case reports of efficacy • Case reports of bleeding or heparin-induced thrombocytopenia associated with pharmacologic strategies • In vitro studies • Animal studies • Cost-effectiveness studies • Modeling studies • Risk assessment studies • Registries without descriptions of interventions • Diagnostic studies • Ecologic study designs • Time-series designs • No original data, commentary, or editorial • Systematic reviews and meta-analysis

• Studies that evaluate interventions or mechanical devices shown in Table 1	• Studies of agents that have not been approved for thromboprophylaxis in the United States or interventions not available in the United States will not be evaluated
• Symptomatic deep vein thrombosis • Symptomatic pulmonary embolism • Mortality • Post-thrombotic syndrome • Quality of life • Length of hospital stay • Lenght of ICU stay • Bleeding (major, minor) • Heparin-induced thrombocytopenia • Allergic reaction • Mechanical device complications • Infections • Asymptomatic deep vein thrombosis • INR, PTT, factor Xa level **(KQs 7 and 8)**	• No data on relevant outcomes of interest
• IVC filters KQs 1, 2a, 3, and 6	

*We anticipate a paucity of randomized controlled trials in these special populations and a paucity of relevant controlled studies for some KQs (KQs 4 and 5). Thus, we plan to include observational studies. However to be eligible for inclusion these studies must be conducted among these special populations and report data on the outcomes of interest against a relevant comparator as shown in the PICOTS Table.

Abbreviations: INR = international normalized ratio; IVC = inferior vena cava; KQ = key question; PTT = partial thromboplastin time; VTE = venous thromboembolism

Since the approval process for medical devices including IVC filters is different from that of pharmacologic agents and does not require proof of safety and efficacy in randomized controlled trials, IVC filters have been evaluated in uncontrolled designs that will be evaluated for inclusion. We plan to include case series and case reports of device complications in the relevant special populations. We also plan to include case reports of pharmacologic therapies other than their known complications of bleeding and heparin-induced thrombocytopenia. We will prioritize evidence strategies regarding study designs for relevant KQs by using a transparent framework.[47] Any subsequent modifications to the inclusion/exclusion criteria of study designs will depend on the availability of relevant studies for each KQ and will be noted as a protocol amendment.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will search the following databases for primary studies: MEDLINE®, EMBASE®, SCOPUS, CINAHL®, www.clinicaltrials.gov, International Pharmaceutical Abstracts (IPA), and the Cochrane Library. We will develop a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of the medical subject headings (MeSH®) terms and text words of key articles identified a priori. The search will be updated during the peer review process. The search strategy for MEDLINE can be found in Appendix A. We will also review the reference lists of all included articles, relevant review articles, and related systematic reviews to identify articles that may have been missed by the database searches. In addition,

we will review the Scientific Information Packets provided by the pharmaceutical manufacturers. The search will not have any language restrictions.[48] We will note the proportion of non-English articles that are potentially eligible and determine whether they will significantly impact the conclusions.

C. Data Abstraction and Data Management

We will use DistillerSR (Evidence Partners, 2010) to manage the screening and review process. DistillerSR is a Web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies are uploaded to the system. Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, abstract review.

Abstracts will be reviewed independently by two investigators and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (Table 3). Differences between investigators regarding abstract inclusion or exclusion will be tracked and resolved through consensus adjudication. Articles promoted on the basis of abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication. We will maintain a list of excluded articles and the potential reasons for exclusion.

We will use a systematic approach to extract the data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis. Each article will undergo double review by study investigators for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles selected by the first two reviewers to ensure consistency in the abstraction of data from the articles. Reviewers will not be masked to the authors, institution, or journal for each article. For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race, comorbidities), eligibility criteria, interventions (e.g., route of administration and dosing), outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability.

All information from the article review process will be entered into the DistillerSR database by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data, as well as to create detailed evidence tables and summary tables.

D. Assessment of Methodological Quality of Individual Studies

The risk of bias of included trials will be conducted independently and in duplicated based on the Cochrane Collaboration's Risk of Bias Tool.[49] For nonrandomized observational studies; we will use the Newcastle Ottawa Scale.[50] Additionally, we plan to use selected items from the McHarm Tool for assessing adverse events.[51] We will supplement these tools with additional quality assessment questions based on recommendations in the Guide for Conducting Comparative Effectiveness Reviews[52] and review the item bank on risk of bias for observational studies.[53] For both the randomized controlled trials and the nonrandomized studies, the overall study quality will be assessed as:

- **Good** (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.

- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

E. Data Synthesis

For each KQ, we will create a set of detailed evidence tables containing all information abstracted from eligible studies. We will conduct meta-analyses when there are sufficient data (at least three studies of the same design) and when studies are sufficiently homogenous with respect to the population characteristics, study duration, and drug dose).

For studies amenable to pooling with meta-analyses, we will calculate pooled mean differences, risk differences or relative risks by using a DerSimonian and Laird random effects model. We will identify statistical heterogeneity between the trials in all the meta-analyses by using: 1) a chi-squared test with a significance level of alpha ≤ 0.10, and 2) an I-squared statistic with a value greater than 50 percent indicating substantial heterogeneity. We will not report the pooled result if substantial heterogeneity is found. We will conduct sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we will conduct formal tests for publication bias by using Begg's and Egger's tests, including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses will be conducted with STATA software (Intercooled, version 11, StataCorp, College Station, TX).

When we are unable to pool studies, we will calculate and display the individual mean differences, risk differences, or relative risks with 95 percent confidence intervals for the individual studies. We will model rare adverse events (<1%) using the Peto odds ratio, which has the best confidence interval coverage for rare events, because the random effects model is statistically underpowered.[54] If we detect an imbalance in trial sizes and the number of zero event studies, we will conduct appropriate sensitivity analyses by using treatment arm continuity correction approachesd.[55]

F. Grading the Evidence for Each Key Question

At the completion of our review, we will grade the quantity, quality, and consistency of the best available evidence addressing KQs 1–8 by adapting an evidence grading scheme recommended in the *Methods Guide for Conducting Comparative Effectiveness Reviews*.[56] In assigning evidence grades we will consider the four required domains including risk of bias of included studies, directness, consistency, and precision. We will also consider additional domains such as biological plausibility, dose-response effect, impact of plausible confounders, and publication bias. Evidence will be graded for the outcomes in the KQs. We will classify evidence pertaining to KQs 1–8 into four basic categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable).

G. Assessing Applicability

Applicability will be assessed separately for the different outcomes of benefit (reduction in VTE) and harm (increased risk of bleeding) for the entire body of evidence guided by the PICOTS framework as recommended in the *Methods Guide for Comparative Effectiveness Reviews of Interventions*.[52] Some potential factors that will be assessed that might limit applicability of these findings from trials designed to assess efficacy of prophylactic agents include whether patients with comorbidities have been excluded,

difference in event rates of VTE, the concomitant use of nonmedical cointerventions (early ambulation) and the choice and dosing of appropriate comparators.

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VI. Definition of Terms

DVT = deep vein thrombosis,
LMWH = low-molecular-weight heparin
PE = pulmonary embolism
UFH = unfractionated heparin
VTE = Venous Thromboembolism
UFH = unfractionated heparin

Special Populations:

For the purpose of this CER we define special populations as those among whom either the benefit or risk of VTE prophylaxis was uncertain or those among whom there is decisional uncertainty about the optimal choice, timing, and dose of VTE prophylaxis and/or significant practice variation due to this uncertainty.

Venous thromboembolism(VTE):

"Pulmonary embolism (PE) resulting from DVT collectively referred to as VTE."[57]
"DVT and PE are collectively known as VTE."[58]
"DVT and PE are commonly grouped together and sometimes referred to as VTE."[59]

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, approaches, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Appendix A.
MEDLINE search strategy via PubMed:

A	B	C
VTE	**Intervention**	**Prevention**
pulmonary	Anticoagulants[mh]	prevent*[tiab]

embolism[mh]		
PE[tiab]	Anticoagulants[tiab]	prophyla*[tiab]
Pulmonary embolism[tiab]	Anticoagulant[tiab]	prevention and control[subheading]
thromboembolism[mh]	Aspirin[mh]	
thromboembolism[tiab]	aspirin[tiab]	
thromboembolisms[tiab]	clopidogrel[nm]	
Thrombosis[mh]	clopidogrel[tiab]	
thrombosis[tiab]	Plavix[tiab]	
DVT[tiab]	ticlopidine[mh]	
VTE[tiab]	ticlopidine[tiab]	
clot[tiab]	ticlid[tiab]	
	prasugrel[nm]	
	prasugrel[tiab]	
	effient[tiab]	
	ticagrelor[nm]	
	ticagrelor[tiab]	
	Brilinta[tiab]	
	cilostazol[nm]	
	cilostazol[tiab]	
	pletal[tiab]	
	warfarin[mh]	
	warfarin[tiab]	
	coumadin[tiab]	
	coumadine[tiab]	
	Dipyridamole[mh]	
	dipyridamole[tiab]	
	persantine[tiab]	
	dicoumarol[mh]	
	dicoumarol[tiab]	
	dicumarol[tiab]	
	Dextran sulfate[mh]	
	dextran sulfate[tiab]	
	“thrombin inhibitors”[tiab]	
	“thrombin inhibitor”[tiab]	
	“direct thrombin inhibitor”[tiab]	
	heparin[mh]	
	Heparin[tiab]	
	Heparins[tiab]	
	LMWH[tiab]	
	LDUH[tiab]	
	Enoxaparin[mh]	
	Enoxaparin[tiab]	
	Lovenox[tiab]	
	Dalteparin[tiab]	
	Fragmin[tiab]	

	Tinzaparin[tiab]	
	innohep[tiab]	
	Nadroparin[tiab]	
	Fondaparinux[nm]	
	Fondaparinux[tiab]	
	Arixtra[tiab]	
	Idraparinux[nm]	
	Idraparinux[tiab]	
	Rivaroxaban[nm]	
	Rivaroxaban[tiab]	
	novastan[tiab]	
	Desirudin[nm]	
	Desirudin[tiab]	
	Iprivask[tiab]	
	Argatroban[nm]	
	Argatroban[tiab]	
	Acova[tiab]	
	Bivalirudin[nm]	
	Bivalirudin[tiab]	
	Angiomax[tiab]	
	Lepirudin[nm]	
	Lepirudin[tiab]	
	Refludan[tiab]	
	Dabigatran[nm]	
	Dabigatran[tiab]	
	Pradaxa[tiab]	
	“factor xa”[mh]	
	“factor Xa”[tiab]	
	vena cava filters[mh]	
	filters[tiab]	
	filter[tiab]	
	compression stockings[mh]	
	intermittent pneumatic compression devices[mh]	
	compression [tiab]	
	“Venous foot pump”[tiab]	

Source: www.effectivehealthcare.ahrq.gov
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